REMARKS

Claims 13-21 and 64 stand rejected under 35 U.S.C. §102(a) as being anticipated by Garbe, Blood Vol. 92, No. 10, Supplement 1, 165a, 1998. Claims 13-21 and 64 stand rejected under 35 U.S.C. §102(e) as being anticipated by Tedder, U.S. Patent No. 5,849,589. Claims 13-21 and 64 stand rejected under 35 U.S.C. §102(e) as being anticipated by Edelson, U.S. Patent No. 5,820,872. Claims 13-20 and 64 stand rejected under 35 U.S.C. §102(b) as being anticipated by Akagawa, et al., Blood 88:4029-4039, 1996. Claims 13-23 and 64 stand rejected under 35 U.S.C. §102(e) as being anticipated by Cohen et al., U.S. Patent No. 6,010,905.

Claims 24-27 stand rejected under 35 U.S.C. §`103(a) as being unpatentable over any one of Cohen, Garbe, Tedder, Edelson or Akagawa, in view of Patel, U.S. Patent No. 5,167,657. Claims 13-27, 46-60 and 64-65 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Edelson, WO 97/34472, in view of any one of Tedder, Cohen or Garbe, and Patel.

Applicant respectfully traverses the Examiner's rejections for the reasons set forth below.

The present claims, as amended, are directed to compositions comprised of functional antigen presenting dendritic cells derived from monocytes treated by exposure to physical perturbation, irradiation in the presence of a photoactivatable agent or treatment with a DNA binding agent. As described in the specification at page 5, lines 1-7, the composition includes a large number of functional dendritic cells generated in a period of only about 6 to 48 hours following treatment of the monocytes. Prior methods of inducing monocyte differentiation into dendritic cells require culturing monocytes

separated from the blood for several days in the presence of special growth factors (cytokines).

The compositions produced by the process as claimed and described in the present application are comprised of dendritic cells that are formed in a relatively short period of time as compared to prior methods. As a result, the dendritic cells of the claimed composition necessarily have a narrow age profile, that is the dendritic cells are relatively similar in their age. In addition, the compositions produced by the process contain a substantially larger population of dendritic cells than cultures incubated for the same time using the prior methods. As set forth in the Declaration of Dr. Richard L. Edelson filed herewith ("Edelson Declaration"), it is known in the art that dendritic cells will phagocytize apoptotic cells during an early period of their life cycle. As a result, the compositions of dendritic cells produced by the process of the present invention can be more efficiently used for immunotherapeutic treatments. Accordingly, because the dendritic cells in the compositions produced by the process of the present invention have a relatively narrow age profile and a larger population of dendritic cells, the composition contains a maximum number of functional, antigen presenting dendritic cells which can be used for immunotherapeutic treatment.

As recited, for example, in claims 13 and 46 and in claims 64 and 65, and described in the specification at, for example, page 9, lines 9-11 and 21-25, in one embodiment of the invention, induction of differentiation of monocytes into functional antigen presenting dendritic cells may be achieved by physical perturbation, such as by passing the monocytes through a narrow diameter plastic channel. The narrow diameter of the channel results in a relatively large surface area to volume ratio. As the monocytes in the fluid come into contact with the surface of the plastic channel, the monocytes repeatedly adhere to the plastic surface and are sheared from the surface by the force of

the fluid flow through the channel. The forces experienced by the monocytes in this process induce a relatively large number of the monocytes to differentiate into functional dendritic cells. Incubation of the composition for 6-48 hours after treatment results in a composition having an enhanced number of functional dendritic cells having a more uniform age profile than compositions produced using prior methods.

As set forth in the Edelson Declaration, the populations of functional dendritic cells in human blood treated using the process of the present invention is substantially higher than the population of dendritic cells in human blood treated using the prior methods described in the references cited by the Examiner. As shown in Table I of the Edelson Declaration, the percentage of cells exhibiting the dendritic cell marker mCD83, which is expressed by dendritic cells at the stage of maturation where the cells are particularly adept at phagocytizing apoptotic cells and processing associated antigens, was approximately four times higher in the composition produced using the process described and claimed in the present application as compared to a composition produced using the prior cell culturing methods for the same period of time. Moreover, the larger population of dendritic cells produced by the process of the present application are all in approximately the same stage of their life cycle, as they are produced after incubation for only 24 hours. This unexpected result provides particular advantages for use of the composition in immunotherapeutic treatment. Production of a large number of functional dendritic cells in this relatively short time period is particularly advantageous for the processing of tumor, or other cellular antigens, derived from freshly isolated sources of disease causing cells. Longer preparatory times for production of functional immature dendritic cells is markedly disadvantageous, at least because of the continued decomposition of apoptotic cells, which become progressively less useful sources of cellular antigens with additional time.

In another aspect, the present invention includes compositions comprised of functional antigen presenting dendritic cells that have been loaded with antigens from disease effector agents for presentation to T cells in the recipient. Apoptotic disease effector agents are presented to the functional dendritic cells, which phagocytize the apoptotic cells and present the antigens from the phagocytized cells at their surface. The monocytes and apoptotic disease effector agents are co-cultivated to maximize the number of functional antigen presenting dendritic cells in the composition.

The data presented in the Edelson Declaration also demonstrate that the compositions produced by the process described in the application can be distinguished from compositions produced using prior methods using well known cell markers. As set forth in Table I in the Edelson Declaration, the compositions produced by the process described in the application have a substantially greater percentage of dendritic cells expressing the cell markers cCD83 and mCD83, which are displayed by maturing dendritic cells.

Applicant has presented evidence demonstrating that the compositions produced by the process described in the application are distinct from the compositions produced by any of the methods described in the references cited by the Examiner. Therefore, applicant has met his burden to overcome the Examiners rejection. See In re Marosi, 710 F.2d 799, 803 (Fed. Cir. 1983)(where product-by-process claim rejected over product produced by another method that appears to be identical, burden is on applicant to produce evidence establishing an unobvious difference); Ex Parte Gray , 10 U.S.P.Q 2d 1922, 1925 (Bd. of Pat. Appeals 1989)(same). Accordingly, for at least the reasons set forth in detail below, claims 13-27, 46-60 and 64-65 are allowable.

Claim Rejections Under 35 U.S.C. § 102

Garbe et al. describes the generation of CDla+ dendritic cells from cultured peripheral monocytes in the presence of IL-4 and GM-CSF. Garbe reports that addition of TGF-β1 within 5 days of culture increased numbers and purity of CD1a+ dendritic cells. Garbe does not describe compositions containing an enhanced number of functional dendritic cells generated in a relatively short period of time of less than 48 hours after treatment of the monocytes.

As stated in the specification, and as evidenced by the data provided in the Edelson declaration, the prior cell culturing techniques utilizing special growth factors such as GM-CSF and IL-4 take longer to induce the monocytes in the culture medium to form dendritic cells than the process of the present invention. The data presented in Table I of the Edelson Declaration shows that a composition produced by the process of the present invention contains substantially more functional dendritic cells than compositions produced using the special growth factors used in the composition produced by the process described in Garbe. Moreover, the dendritic cells in the compositions produced by the process of the present invention are produced in over a much shorter time period (less than 48 hours) than the dendritic cells produced by the prior methods. Accordingly, the composition claimed in the present invention necessarily contains dendritic cells that are of a relatively uniform age as compared to the compositions produced by the process described in Garbe.

The data set forth in the Edelson Declaration also show that the known cell markers for dendritic cells, cCD83 and mCD83, can be used to distinguish the compositions produced by the method of the present invention from compositions produced using prior methods. Compositions produced by the process of the present

invention contain dendritic cell populations with substantially higher percentage of cells displaying the cell marker mCD83.

In the Office Action, the Examiner's rejection was based in part on a lack of factual evidence indicating that the dendritic cells in the composition disclosed by Garbe are not as effective in presenting antigens as the dendritic cells in the claimed composition. Applicant has not argued that the individual dendritic cells are more or less effective in presenting antigens. Rather, applicant argues that the claimed composition is more effective for immunotherapeutic treatment because the composition contains a greater number of antigen presenting dendritic cells at an optimal stage of maturation for processing and presenting antigens from apoptotic cells. The data set forth in Table I of the Edelson Declaration present evidence supporting this argument, as the population of cells expressing mCD83 was four times greater in the composition produced by the process described in the present application as compared to a composition produced by the prior method, such as that of Garbe. Accordingly, the claimed composition is more effective in presenting antigens, the composition is not physically the same as the composition described in Garbe, and the composition has different properties than the composition described in Garbe. Therefore, Garbe does not anticipate the composition of claims 13-21 and 64 of the present invention.

Similarly, Tedder et al., U.S. Patent No. 5,849,589 describes a method for inducing monocyte differentiation into dendritic cells using a culture medium containing CM-CSF and IL-4. While Tedder describes various improvements in these cell culturing methods, including the use of TNF-α in the culture medium, the compositions formed in the cell cultures described by Tedder all required at least several days to form. See Col. 5, lines 6-54. For example, Tedder states that "TNF-α-induced differentiation of blood monocytes cultured with GM-CSF and IL-4 generated dendritic-like cells within 7-9

days." Col. 5, lines 51-54. Tedder does not teach or suggest a composition containing dendritic cells produced in a relatively short time in which the age of the dendritic cells is relatively uniform. Accordingly, Tedder does not anticipate the composition of claims 13-21 and 64 of the present invention.

Edelson, U.S. Patent No. 5,820,872, ("the Edelson '872 patent") describes methods for producing cellular vaccines containing a plurality of solid tumor derived antigens admixed with antigen presenting cells. The method described in the Edelson '872 patent does not involve the induction of dendritic cells at all, but merely the induction of empty class I MHC molecules at the surface of antigen presenting cells already present in the subject's blood. Those empty class I MHC molecules are created by holding the antigen presenting cells at a lower-than-body temperature, thereby causing transport to the cell surface of empty, rather than filled, class I MHC molecules. See, e.g. Col. 6, lines 16-22. The tumor derived antigens can be externally loaded into the empty MHC molecules on the surface of the leukocytes for presentation of the antigen to T cells in the immune system.

The Edelson '872 patent does not teach or suggest the use of functional dendritic cells in the treatment described, and the Edelson '872 patent does not teach or suggest a method for producing dendritic cells. Most importantly, the Edelson '872 patent does not teach or suggest incubation of blood for any period of time following treatment by photopheresis to allow differentiation of monocytes into dendritic cells. Accordingly, the Edelson '872 patent does not anticipate the composition of claims 13-21 and 64 of the present invention.

Akagawa et al. describe the generation of dendritic cells from monocytes by culturing the monocytes in growth factors GM-CSF and IL-4 for seven days. As shown by the data set forth in Table I of the Edelson Declaration, compositions produced by the

process of the present application contain a larger number of dendritic cells as compared to compositions produced in the growth factors GM-CSF and IL-4. Akagawa nowhere describes the population of dendritic cells expressing the mCD83 cell marker produced by the culturing method, and Akagawa does not teach or suggest a method for inducing monocyte differentiation in a relatively short period of time to produce dendritic cells having a relatively uniform age profile. Akagawa does not teach or suggest a composition containing an optimum number of functional antigen presenting dendritic cells such as the compositions recited in claims 13-20 and 64 of the present invention. Accordingly, Akagawa does not anticipate the composition of claims 13-20 and 64 of the present invention.

Cohen et al. describes methods for increasing the antigen presenting ability of blood monocytes by increasing the intracellular calcium level to cause the monocytes to convert to functional dendritic cells. Accordingly, the dendritic cells in the composition produced by the method described by Cohen necessarily have an increased cellular calcium concentration as compared to the dendritic cells produced by the process of the present invention, which does not involve increasing cellular calcium levels. Therefore, compositions produced by the process described in Cohen are inherently distinguishable from compositions produced by the process described in the present invention. Accordingly, the Cohen reference does not anticipate the composition of claims 13-23 and 64 of the present invention.

Response to Claim Rejections Under 35 U.S.C. § 103

Patel, U.S. Patent No. 5,167,657, describes a plastic composition that can be used for the production of blood bags. As recognized by the applicant, blood bags of the type described in Patel were previously known in the art. The Patel reference does not discuss in any way the production of antigen presenting dendritic cells, the loading of dendritic

cells with antigens, or the use of antigen presenting dendritic cells in immunotherapeutic treatment. The Examiner agrees with the Applicant that the Patel reference does not add anything to the teachings of Garbe, Tedder, Edelson, Akagawa or Cohen regarding the compositions set forth in claims 24-27. For the reasons described above, these references do not teach or suggest the compositions that are contained in the packaged preparations recited in claims 24-27. Accordingly, it is respectfully submitted that claims 24-27 are unobvious over Patel in view of Garbe, Tedder, Edelson, Akagawa or Cohen.

Edelson (WO97/34472) describes a method for extracorporeal treatment of blood to enhance the subject's immune system response, essentially a nonspecific adjuvant stimulatory effect. In the method described in the Edelson (WO97/34472) reference, extracorporeal blood is treated using photopheresis to enhance MHC expression on the cell surface. The Edelson (WO97/34472) reference does not teach or suggest the use of physical perturbation, such as contacting monocytes with plastic surfaces as described in the Edelson Declaration, to induce differentiation of monocytes into functional dendritic cells. More importantly, there is nothing in the Edelson (WO97/34472) reference that teaches or suggests incubation of the blood for any time period following treatment by photopheresis, much less a teaching or suggestion to incubate the treated blood for a sufficient time to allow differentiation of monocytes to functional dendritic cells. The Edelson (WO97/34472) reference does not add anything to the teachings of Garbe, Tedder, Edelson, Akagawa or Cohen regarding the compositions set forth in claims 13-27, 46-60 and 64-65. Moreover, there is nothing in the Edelson (WO97/34472) reference that suggests that the method described in the Edelson '872 patent may be modified to produce functional antigen presenting dendritic cells by incubating the blood following treatment by photopheresis. Accordingly, the Edelson (WO97/34472) reference in combination with Garbe, Tedder or Cohen and Patel would not teach or suggest to one of

ordinary skill in the art the compositions set forth in claims 13-27 and 46-60 of the present application, and the combined teachings of those references do not describe a process for producing a composition having the characteristics of the claimed composition.

Conclusion

In view of the foregoing, it is respectfully submitted that claims 13-27, 46-60 and 64-65 are allowable. Accordingly, favorable action on this application is requested at the earliest possible date. Should the Examiner have any questions regarding this Response or should the Examiner wish to discuss this case further, the Examiner is urged to contact the undersigned attorney at the telephone number listed.

A Petition and Fee for Extension of Time Under 37 C.F.R. § 1.136(a)(1) is filed herewith requesting an extension of time to respond to the Office Action from February 7, 2002 to May 7, 2002. A Request for Continued Examination and the associated fee is also being filed herewith. Accordingly, no additional fees are believed to be required. However, if an additional fee is required, or to cover any deficiencies in fees paid, authorization is hereby given to charge our deposit account no. 50-1631.

Respectfully submitted,

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By 

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